Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently Amended) A ligand screening apparatus which screens for a ligand that binds to a protein when coordinate data of the protein of single chain or plural chains is given, the apparatus comprising:

a post-structural-change protein coordinate data selecting unit that ~~effects~~ conducts structural change ~~in consideration of~~ in the coordinate data of the protein while considering dynamic behavior, wherein said structural change is performed using an induced-fit parameter reflecting induced fit on the coordinate data of the protein and ~~selects~~ post-structural-change protein coordinate data is selected;

a spatial point designating unit that designates a spatial point at which superposition with the ligand is to be conducted from the post-structural-change protein coordinate data selected by the post-structural-change protein coordinate data selecting unit;

an interaction function calculating unit that calculates an interaction function when the protein and the ligand bind to each other using the spatial point designated by the spatial point designating unit and a ligand coordinate data of the ligand; and

a ligand evaluating unit that evaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating unit.

2. (Previously Presented) The ligand screening apparatus according to claim 1, wherein the interaction function calculating unit calculates the interaction function using Sscore(i,j) shown in Formula 1:

$$Sscore(i,j)=\sum_{ij}^{\lambda}\begin{cases}\text{when i is not equal to j}\\ \alpha\times\left[\exp\left\{-\left(d_{ij}^{s}-d_{ij}^{c}\right)^{2}\right\}-\beta\right]\Big/\dfrac{\left(d_{ij}^{s}+d_{ij}^{c}\right)^{2}}{2}\\ \text{when i is equal to j}\\ \alpha\times(1-\beta)\end{cases}$$ [Formula 1]

wherein d_{ij}^{s} is a distance between i-th spatial point and j-th spatial point in the target protein, d_{ij}^{C} is an interatomic distance between i-th atom and j-th atom in a compound, α is a coefficient for making Sscore(i,j) the maximum value when the group of spatial points in the target protein and the compound completely overlap with each other, β is a coefficient for giving a threshold value by which it can be defined as "overlapping".

3. (Previously Presented) The ligand screening apparatus according to claim 1, wherein the interaction function calculating unit further comprises an interaction function optimizing unit that carries out optimization so as to make the score of interaction function maximum.

4. (Previously Presented) The ligand screening apparatus according to claim 3, wherein the interaction function calculating unit further comprises:

an interaction energy optimizing unit that calculates interaction energy with the protein for the superposed ligand after optimization of the interaction function by the interaction function optimizing unit, and optimizes the interaction energy while finely adjusting conformation of ligand 3D structure data.

5. (Previously Presented) The ligand screening apparatus according to claim 4, wherein the ligand evaluating unit further comprises:

a reevaluating unit that causes execution of the interaction function calculating unit after largely changing conformation of ligand 3D structure data following optimization by the interaction energy optimizing unit, and reevaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating unit.

6. (Previously Presented) The ligand screening apparatus according to claim 1, wherein in calculation of any one of the induced-fit parameter and the post-structural-change protein coordinate data or both, the post-structural-change protein coordinate data selecting unit calculates a normal mode for the protein coordinate data, determines intensity of fluctuation of each amino acid, and conducts a molecular dynamic calculation using the intensity of fluctuation as a constraint condition.

7. (Currently Amended) The ligand screening apparatus according to claim 6, wherein the post-structural-change protein coordinate data selecting unit calculates a fluctuation value of a dihedral angle of a main chain according to normal mode calculation, and conducts a molecular dynamic calculation while setting the fluctuation value as a coefficient of force K in the molecular dynamic calculation shown by Formula 2 or Formula 3:

$$Erot = Krot(\phi - \phi 0)^2 \qquad \text{[Formula 2]}$$

wherein Erot represents energy of a dihedral angle of a main chain atom in a 3D structure of a protein, ϕ represents a dihedral angle of the main chain atom, $\phi 0$ represents a standard value of the dihedral angle of the main chain atom, when a value of Krot (a coefficient of force) is large, ϕ is constrained by $\phi 0$[[.]],

$$Epos = Kpos(r - r0)^2 \qquad \text{[Formula 3]}$$

wherein Epos represents position energy of the main chain atom in a 3D structure of a protein, r represents a coordinate of the main chain atom, r0 represents a standard value of the coordinate of the main chain atom, when a value of Kpos (a coefficient of force) is large, r is constrained by r0.

8. (Withdrawn) The ligand screening apparatus according to claim 1, wherein the interaction function calculating unit uses the interaction function to which a dynamic property function representing dynamic property of protein is added as "elastic energy".

9. (Withdrawn) The ligand screening apparatus according to claim 8, wherein the interaction function calculating unit adapts "U collision" as "elastic energy" which is a function shown by Formula 4 in consideration of local flexibility of the protein

$$U_{collision} = \sum_{i=1}^{M} \sum_{j=1}^{N} \varphi(i,j)$$

$$\varphi(i,j) = \text{Kcollision} * (\text{Rcollision}(i,j) - R)^2$$

[Formula 4]

wherein M is a number of atoms in an active site that prohibit collision, N is a number of atoms of the ligand, interatomic distance R between an i-th atom of a main chain or a side chain with a little dynamic behavior in an active site, and a j-th atom in the ligand is not more than collision distance "Rcollision(i,j)", $\phi(i,j)$ is calculated.

10. (Previously Presented) The ligand screening apparatus according to claim 1, wherein the interaction function calculating unit uses the interaction function to which a normal mode analysis result or secondary structure determination result of the protein is added as a dynamic property function that represents a dynamic property of the protein.

11. (Currently Amended) A ligand screening method which screens for a ligand that binds to a protein when coordinate data of the protein of single chain or plural chains is given, the method comprising:

a post-structural-change protein coordinate data selecting step that ~~effects~~ conducts, with a computer, structural change ~~in consideration of~~ in the coordinate data of the protein while considering dynamic behavior, wherein said structural change is performed using an induced-fit parameter reflecting induced fit on the coordinate data of the protein and ~~selects~~ post-structural-change protein coordinate data is selected;

a spatial point designating step that designates a spatial point at which superposition with the ligand is to be conducted from the post-structural-change protein coordinate data selected by the post-structural-change protein coordinate data selecting step;

an interaction function calculating step that calculates an interaction function when the protein and the ligand bind to each other using the spatial point designated by the spatial point designating step and a ligand coordinate data of the ligand; and

a ligand evaluating step that evaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating step;

wherein the interaction function calculating step calculates the interaction function using Sscore(i,j) shown in Formula 1:

$$Sscore(i,j)=\sum_{ij}^{\lambda}\begin{cases}\text{when i is not equal to j} \\ \alpha\times\left[\exp\left\{-\left(d_{ij}^{s}-d_{ij}^{c}\right)^{2}\right\}-\beta\right] \Big/ \dfrac{\left(d_{ij}^{s}+d_{ij}^{c}\right)^{2}}{2} \\ \text{when i is equal to j} \\ \alpha\times(1-\beta)\end{cases} \quad \text{[Formula 1]}$$

wherein d_{ij}^{s} is a distance between i-th spatial point and j-th spatial point in the target protein, d_{ij}^{C} is an interatomic distance between i-th atom and j-th atom in a compound, α is a coefficient for making Sscore(i,j) the maximum value when the group of spatial points in the target protein and the compound completely overlap with each other, β is a coefficient for giving a threshold value by which it can be defined as "overlapping".

12. (Cancelled)

13. (Previously Presented) The ligand screening method according to claim 11, wherein the interaction function calculating step further comprises an interaction function optimizing step that carries out optimization so as to make the score of interaction function maximum.

14. (Previously Presented) The ligand screening method according to claim 13, wherein the interaction function calculating step further comprises:

an interaction energy optimizing step that calculates interaction energy with the protein for the superposed ligand after optimization of the interaction function by the interaction function optimizing step, and optimizes the interaction energy while finely adjusting conformation of ligand 3D structure data.

15. (Previously Presented) The ligand screening method according to claim 14, wherein the ligand evaluating step further comprises:

a reevaluating step that causes execution of the interaction function calculating step after largely changing conformation of ligand 3D structure data following optimization by the interaction energy optimizing step, and reevaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating step.

16. (Previously Presented) The ligand screening method according to claim 11, wherein in calculation of any one of the induced-fit parameter and the post-structural-change protein coordinate data or both, the post-structural-change protein coordinate data selecting step calculates a normal mode for the protein coordinate data, determines intensity of fluctuation of each amino acid, and conducts a molecular dynamic calculation using the intensity of fluctuation as a constraint condition.

17. (Currently Amended) The ligand screening method according to claim 16, wherein the post-structural-change protein coordinate data selecting step calculates a fluctuation value of a dihedral angle of a main chain according to normal mode calculation, and conducts a molecular dynamic calculation while setting the fluctuation value as a coefficient of force K in the molecular dynamic calculation shown by Formula 2 or Formula 3:

$$Erot = Krot(\phi - \phi 0)^2 \qquad \text{[Formula 2]}$$

wherein Erot represents energy of a dihedral angle of a main chain atom in a 3D structure of a protein, ϕ represents a dihedral angle of the main chain atom, $\phi 0$ represents a standard value of the dihedral angle of the main chain atom, when a value of Krot (a coefficient of force) is large, ϕ is constrained by $\phi 0$[[.]].

$$Epos = Kpos(r - r0)^2 \qquad \text{[Formula 3]}$$

wherein Epos represents position energy of the main chain atom in a 3D structure of a protein r represents a coordinate of the main chain atom, r0 represents a standard value of the coordinate of the main chain atom, when a value of Kpos (a coefficient of force) is large, r is constrained by r0.

18. (Withdrawn) The ligand screening method according to claim 11, wherein the interaction function calculating step uses the interaction function to which a dynamic property function representing dynamic property of protein is added as "elastic energy".

19. (Withdrawn) The ligand screening method according to claim 18, wherein the interaction function calculating step adapts "U collision" as "elastic energy" which is a function shown by Formula 4 in consideration of local flexibility of protein:

$$U_{collision} = \sum_{i=1}^{M}\sum_{j=1}^{N}\varphi(i,j)$$
$$\varphi(i,j) = Kcollision * (Rcollision(i,j) - R)^2 \qquad \text{[Formula 4]}$$

wherein M is a number of atoms in an active site that prohibit collision, N is a number of atoms of ligand, interatomic distance R between an i-th atom of a main chain or a side chain with a little dynamic behavior in an active site, and a j-th atom in the ligand is not more than collision distance "Rcollision(i,j)", ϕ(i,j) is calculated.

20. (Previously Presented) The ligand screening method according to claim 11, wherein the interaction function calculating step uses the interaction function to which a normal mode analysis result or secondary structure determination result of the protein is added as a dynamic property function that represents a dynamic property of the protein.

21. (Currently Amended) A non-transitory computer-readable medium having a program which makes a computer execute a ligand screening method which screens for a ligand that binds to a protein when coordinate data of the protein of single chain or plural chains is given, the method comprising:

a post-structural-change protein coordinate data selecting step that ~~effects~~ conducts structural change ~~in consideration of~~ in the coordinate data of the protein while considering dynamic behavior, wherein said structural change is performed using an induced-fit parameter reflecting induced fit on the coordinate data of the protein and ~~selects~~ post-structural-change protein coordinate data is selected;

a spatial point designating step that designates a spatial point at which superposition with the ligand is to be conducted, from the post-structural-change protein coordinate data selected by the post-structural-change protein coordinate data selecting step;

an interaction function calculating step that calculates an interaction function when the protein and the ligand bind to each other using the spatial point designated by the spatial point designating step and a ligand coordinate data of the ligand; and

a ligand evaluating step that evaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating step;

wherein the interaction function calculating step calculates the interaction function using Sscore(i,j) shown in Formula 1

$$Sscore(i,j)=\sum_{ij}^{\lambda}\begin{cases}\text{when i is not equal to j} \\ \alpha\times\left[\exp\left\{-\left(d_{ij}^{s}-d_{ij}^{c}\right)^{2}\right\}-\beta\right] \Big/ \dfrac{\left(d_{ij}^{s}+d_{ij}^{c}\right)^{2}}{2} \\ \text{when i is equal to j} \\ \alpha\times(1-\beta)\end{cases} \quad \text{[Formula 1]}$$

wherein d_{ij}^{s} is a distance between i-th spatial point and j-th spatial point in the target protein, d_{ij}^{C} is an interatomic distance between i-th atom and j-th atom in a compound, α is a

coefficient for making Sscore(i,j) the maximum value when the group of spatial points in the target protein and the compound completely overlap with each other, β is a coefficient for giving a threshold value by which it can be defined as "overlapping".

22. (Cancelled)

23. (Previously Presented) The non-transitory computer-readable medium having a program according to claim 21, wherein the interaction function calculating step further comprises an interaction function optimizing step that carries out optimization so as to make the score of interaction function maximum.

24. (Previously Presented) The non-transitory computer-readable medium having a program according to claim 23, wherein the interaction function calculating step further comprises:

an interaction energy optimizing step that calculates interaction energy with the protein for the superposed ligand after optimization of the interaction function by the interaction function optimizing step, and optimizes the interaction energy while finely adjusting conformation of ligand 3D structure data.

25. (Previously Presented) The non-transitory computer-readable medium having a program according to claim 24, wherein the ligand evaluating step further comprises:

a reevaluating step that causes execution of the interaction function calculating step after largely changing conformation of ligand 3D structure data following optimization by the interaction energy optimizing step, and reevaluates the ligand that binds to the protein based on the interaction function calculated by the interaction function calculating step.

26. (Previously Presented) The non-transitory computer-readable medium having a program according to claim 21, wherein in calculation of any one of the induced-fit parameter and the post-structural-change protein coordinate data or both, the post-structural-change protein coordinate data selecting step calculates a normal mode for the protein coordinate data, determines intensity of fluctuation of each amino acid, and conducts a molecular dynamic calculation using the intensity of fluctuation as a constraint condition.

27. (Currently Amended) The non-transitory computer-readable medium having a program according to claim 26, wherein the post-structural-change protein coordinate data selecting step calculates a fluctuation value of a dihedral angle of a main chain according to the normal mode calculation, and conducts the molecular dynamic calculation while setting the fluctuation value as a coefficient of force K in the molecular dynamic calculation shown by Formula 2 or Formula 3:

$$\mathrm{Erot} = \mathrm{Krot}(\phi - \phi 0)^2 \qquad \text{[Formula 2]}$$

wherein Erot represents energy of a dihedral angle of a main chain atom in a 3D structure of a protein, ϕ represents the dihedral angle of the main chain atom, $\phi 0$ represents a standard value of the dihedral angle of the main chain atom, when a value of Krot (a coefficient of force) is large, ϕ is constrained by $\phi 0$[[.]].

$$\mathrm{Epos} = \mathrm{Kpos}(\mathrm{r} - \mathrm{r}0)^2 \qquad \text{[Formula 3]}$$

wherein Epos represents a position energy of the main chain atom in 3D structure of a protein, r represents a coordinate of the main chain atom, r0 represents a standard value of the coordinate of the main chain atom, when a value of Kpos (a coefficient of force) is large, r is constrained by r0.

28. (Withdrawn) The program according to claim 21, wherein the interaction function calculating step uses the interaction function to which a dynamic property function representing dynamic property of protein is added as "elastic energy".

29. (Withdrawn) The non-transitory computer-readable medium having a program according to claim 28, wherein the interaction function calculating step adapts "U collision" as "elastic energy" which is a function shown by Formula 4 in consideration of local flexibility of protein:

$$\mathrm{U}_{\mathrm{collision}} = \sum_{i=1}^{M}\sum_{j=1}^{N}\varphi(i,j)$$

$$\varphi(i,j) = \mathrm{Kcollision} * (\mathrm{Rcollision}(i,j) - R)^2$$

[Formula 4]

wherein M is a number of atoms in an active site that prohibit collision, N is a number of atoms of ligand, interatomic distance R between an i-th atom of a main chain or a side chain with a little dynamic behavior in active site, and a j-th atom in the ligand is not more than collision distance "Rcollision(i,j)", $\phi(i,j)$ is calculated.

30. (Previously Presented) The non-transitory computer-readable medium having a program according to claim 21, wherein the interaction function calculating step uses the interaction function to which a normal mode analysis result or secondary structure determination result of the protein is added as a dynamic property function that represents a dynamic property of the protein.

31. (Cancelled)